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A detailed description of the phenotypic spectrum of North Sea Progressive Myoclonus Epilepsy in a large cohort of seventeen patients

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ABSTRACT

Introduction: In 2011, a homozygous mutation in *GOSR2* (c.430G > T; p. Gly144Trp) was reported as a novel cause of Progressive Myoclonus Epilepsy (PME) with early-onset ataxia. Interestingly, the ancestors of patients originate from countries bound to the North Sea, hence the condition was termed North Sea PME (NSPME). Until now, only 20 patients have been reported in literature. Here, we provide a detailed description of clinical and neurophysiological data of seventeen patients.

Methods: We collected clinical and neurophysiological data from the medical records of seventeen NSPME patients (5–46 years). In addition, we conducted an interview focused on factors influencing myoclonus severity.

Results: The core clinical features of NSPME are early-onset ataxia, myoclonus and seizures, with additionally areflexia and scoliosis. Factors such as fever, illness, heat, emotions, stress, noise and light (flashes) all exacerbated myoclonic jerks. Epilepsy severity ranged from the absence of or incidental clinical seizures to frequent daily seizures and status epilepticus. Some patients made use of a wheelchair during their first decade, whereas others still walked independently during their third decade. Neurophysiological features suggesting neuromuscular involvement in NSPME were variable, with findings ranging from indicative of sensory neuronopathy and anterior horn cell involvement to an isolated absent H-reflex.

Conclusion: Although the sequence of symptoms is rather homogeneous, the severity of symptoms and rate of progression varied considerably among individual patients. Common triggers for myoclonus can be identified and myoclonus is difficult to treat; to what extent neuromuscular involvement contributes to the phenotype remains to be further elucidated.

1. Introduction

In 2011, a homozygous mutation in the Golgi SNAP Receptor Complex Member 2 (*GOSR2)* gene was described as a new cause of Progressive Myoclonus Epilepsy (PME) with early ataxia [1]. It was [2] subsequently reported that ancestors of patients with this mutation came from countries bounding to the North Sea, hence the condition was termed 'North Sea' PME (NSMPE). All patients carried the same homozygous missense mutation in *GOSR2* (c.430G > T, p.Gly144Trp), a gene encoding a trafficking membrane protein involved in the fusion of vesicles from the endoplasmic reticulum to the cis- Golgi [3]. The pathogenicity of the p.Gly144Trp mutation so far relies on in vitro

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studies with yeast in which a mutation in *bos1,* the yeast ortholog of *GOSR2*, demonstrated evidence for a (partial) loss of function. Until now, the underlying mechanism of the homozygous *GOSR2* mutation leading to PME with early-onset ataxia is largely unknown.

The clinical picture of NSPME is characterized by the onset of ataxia and areflexia at a young age, typically followed by the onset of myoclonus and epilepsy. Deformities such as scoliosis and a (slightly) elevated creatine kinase (CK) level may additionally be found, but are not present in every patient. Interestingly, cognitive function appears to be relatively spared, but NSPME is a very debilitating neurological condition with a progressive nature, and treatment modalities are currently only symptomatic [1,3–6].

NSPME is part of the group of PMEs, which are rare genetic disorders characterized by myoclonus, seizures, and progressive neurological deterioration, particularly ataxia and dementia [7]. The clinical phenotype of PME overlaps with progressive myoclonus ataxia (PMA), which usually has a genetic cause as well. PMA is defined as progressive myoclonus and ataxia, but without prominent dementia and with infrequent seizures [8,9]. Based on the NSPME phenotype one can debate whether it is in fact a PME or PMA phenotype (Van Egmond et al. [4]).

Although most patients reported to date carry the *GOSR2* mutation in homozygous form, recently, the spectrum of observed *GOSR2* mutations has expanded. One compound heterozygous *GOSR2* mutation (c.430G > T and c.491_493delAGA) results in a similar clinical phenotype with a somewhat milder disease course compared to NSPME [10]. Interestingly, two other compound heterozygous *GOSR2* mutations (c.430G > T and c.336 + 1G > A; c.430G > T and c. 2T > G) were linked to muscular dystrophy [11,12]. This shows that *GOSR2* mutations can be associated with a broader phenotypic spectrum, and may suggest that the GOSR2 protein has a function in several organ-systems.

So far, only 20 NSPME patients have been described [1,2,4,5]. Here, we provide a detailed clinical description of a large NSPME cohort (n = 17) with the aim of further delineating the clinical phenotype and functioning of patients. As two other *GOSR2* mutations were associated with muscular dystrophy, we closely looked into possible neuromuscular involvement in NSPME in this cohort.

2. Patients and methods

We included all patients with NSPME from three medical centers, encompassing nine patients previously reported (Boissé Lomax et al., Van Egmond et al., Anderson et al. [2,4,5]) and eight new cases. Fourteen patients were Dutch and three South African, ancestors of the South African patients originated from Northern Germany. All patients or their parents consented to participate and the study was performed in accordance with regulations of the Human Research Ethics Committees of the University Medical Center Groningen (UMCG), Erasmus Medical Center Rotterdam (Erasmus MC) and Wits University Donald Gordon Medical Center Johannesburg (UMCG M17.215724 and M18.235646, Erasmus MC MEC-2018-1136, Wits University M1811121).

We systematically collected data from the medical records on initial presenting signs, motor symptoms, epilepsy, skeletal deformities, highest CK, brain MRI, clinical neurophysiological investigations and treatment. We interviewed caregivers about the onset of signs and symptoms during the last visit of most patients (n = 13). In addition, we interviewed all patients and/or their caregivers about factors that influenced myoclonus severity.

In order to get more insight into neuromuscular involvement in NSPME, we collected information regarding nerve conduction studies (NCS) and needle electromyography (EMG). Data on follow-up NCS and needle EMG were recorded when available. Parameters of NCS included amplitudes of Sensory Nerve Action Potentials (SNAPs) and Compound Muscle Action Potentials (CMAPs), and conduction velocities of SNAPs and CMAPs of patients that underwent conventional warm-up procedures prior to NCS (n = 6/10); and late responses including soleus H-reflexes and ulnar, median, tibial and peroneal F-waves. Parameters of needle EMG included spontaneous muscle activity, duration, amplitude and shape of Motor Unit Action Potentials (MUAPs) and their recruitment pattern.

We used SPSS statistics version 23 (Windows) for descriptive statistics regarding the frequency and mean age onset of symptoms in this NSPME cohort.

3. Results

We included four pediatric patients and thirteen adult patients with NSPME (6 female:11 male). Mean age was 25,4 years (range 5–46 years). The homozygous *GOSR2* mutation (c.430G > T, p.Gly144Trp) was confirmed in fifteen patients. In two patients, genetic analysis for the homozygous *GOSR2* mutation has not been performed, because the mutation was confirmed in their siblings. Supplementary Table 1 displays clinical characteristics and treatment for all patients.

3.1. Clinical characteristics

Fig. 1 summarizes the clinical course of NSPME with the main clinical features over time. In most patients (16/17; 94%), first signs were already noticed by parents around the age of 1–4 years and included delayed motor development (predominantly delayed walking), clumsiness, gait disorders, frequent falls, hypotonia, and jerks (all based on history taking and clinical examination). In six of these patients, their first signs were associated with a period of intercurrent illness/fever. Initial signs were not fully documented for one patient.

Ataxia was first observed on average around the age of 4 years (range 2–8 years) and was present in all patients. Thereafter myoclonus started around the age of 6 years (range 3–9 years) and is also present in all patients. Myoclonus was either generalized or multifocal, present at rest and action-induced, and stimulus-sensitive. The upper limbs were more affected than lower limbs, and myoclonus was most prominent distally in the hands and fingers. In the face, myoclonus was noted around the mouth and tongue. Specific triggers, in particular fever, illness, heat, emotions, stress, noise and light (flashes) all exacerbated myoclonic jerks. Many patients (13/17; 76%) reported that myoclonus exacerbated during the night or early in the morning, especially at waking up.

Most patients developed epileptic seizures over time (n = 15/17; 88%), commonly before their second decade. In one patient, febrile seizures manifested prior to the diagnosis of myoclonus. Seizure types

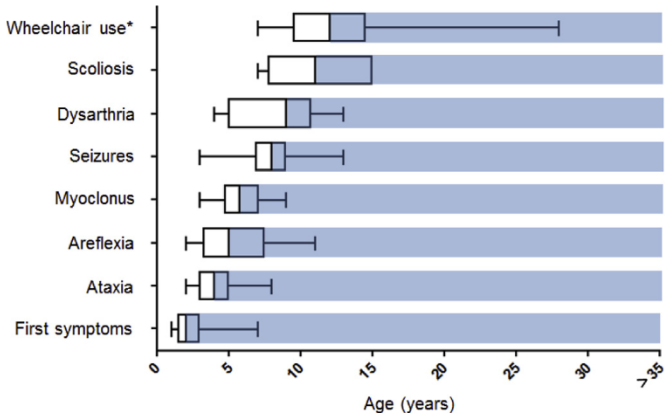

Fig. 1. Sequence of clinical features in NSPME over time, displaying the age at which clinical features were first documented. The colored bar depicts the duration of clinical features. *Age at which patients first started to use a wheelchair. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

included both generalized motor seizures (tonic-clonic and myoclonic) and generalized non-motor seizures (absences). Some patients (4/17; 24%) reported that in the days preceding a seizure, the intensity of myoclonus increased and temporarily decreased after a seizure. Seizure frequency was very variable among the patients with seizures, ranging from daily to yearly seizures and often depended on environmental factors, e.g. stress and days with many activities.

Dysarthria (n = 15) manifested mostly during the first decade. Swallowing problems were reported in 7/17 (41%) patients around their second or third decade. In general, no prominent dementia was reported in the context of severe neurological decline on motor domains. However, in only one patient a full neuropsychological examination was performed at the age of 23 years; demonstrating visual-memory difficulties, working-memory difficulties and poor fluency with intact emotion-recognition and planning skills.

Absent reflexes were reported in all patients, frequently already documented between the age of 2–5 years (n = 9/17; 53%). Areflexia was not accompanied by muscle weakness and disturbed sensory function at a young age.

Scoliosis was documented in 11/17 (65%) patients during their first or second decade. Other deformities included pes cavus (n = 5), pes planus (n = 1), pes varus (n = 1) and syndactyly (n = 1). Hypothyroidism was diagnosed in 3/17 (18%) patients (at ages 17–29 years) and treated with levothyroxine in all three.

3.2. Daily functioning

Most patients used a wheelchair (n = 15/17; 88%), either occasionally (e.g. for long distances) or regularly. The age at which patients first started using a wheelchair ranged from 7 to 28 years. Reasons for starting to use a wheelchair included frequent falls, disturbed balance and myoclonic jerks. Over time, patients reported to have difficulties with eating and drinking, and expressed the need for assistance in many activities of daily life, not only with feeding, but also showering and getting dressed, in line with the progressive nature of the disorder.

3.3. Neurophysiological studies and imaging

3.3.1. Nerve conduction studies and needle electromyography

Previously, Van Egmond et al. [4] reported findings indicating sensory neuronopathy and anterior horn cell involvement in NSPME patients. Here, the follow-up of these patients (n = 5) and findings of new patients are described (n = 5). Supplementary Table 2 displays NCS and needle EMG details.

Sensory and motor NCS were available for 10/17 patients (59%). In 4/10, decreased SNAP amplitudes of upper limbs (median, ulnar and radial nerves) and lower limbs (peroneal and sural nerves) were found without a length-dependent distribution. SNAP conduction velocities were in the normal range to slightly decreased, but in none of the patients (n = 6/10) in the demyelinating range based on their most recent NCS (defined < 75% of the lower limit of the reference range). The decreased SNAP amplitudes could fit a sensory polyneuropathy or sensory neuronopathy. However, based on an absent length-dependent distribution of decreased SNAP amplitudes, a sensory neuronopathy was suspected in 4/10. Motor NCS demonstrated normal or slightly reduced CMAP amplitudes and conduction velocities. F-waves were present in all patients and showed no abnormalities. Motor NCS abnormalities were less pronounced than sensory NCS abnormalities and were discrepant with needle EMG findings. Noticeably, H-reflexes were absent in all patients in which this was tested (n = 9). In one patient, a focal neuropathy of the peroneal nerve was found on NCS.

In 6/10 patients, needle EMG was also available. In 5/6, needle EMG demonstrated broad polyphasic MUAPs with high amplitudes and a decreased recruitment pattern (patients ages 12–36 years) in the tibialis anterior muscle, without spontaneous muscle activity. This was interpreted as a neurogenic pattern, which could fit with sensorimotor polyneuropathy or anterior horn cell involvement. In three patients with an aberrant needle EMG, other muscles were additionally tested, demonstrating a similar neurogenic pattern without a proximal-distal distribution. In view of the absence of a proximal-distal distribution, anterior horn cell involvement was suspected in 3/10. In one patient, no significant needle EMG abnormalities were reported at age 13 years.

Follow-up NCS were available in five patients, demonstrating non-conclusive fluctuating SNAP amplitudes over time in 4/5. In one patient, follow-up NCS data was insufficient for interpretation. Follow-up needle EMGs were available in three patients, demonstrating a slight increase of the neurogenic pattern in 2/3.

In summary, NCS available in ten patients were indicative of sensory neuronopathy (n = 4) and a focal neuropathy (n = 1), and needle EMG findings available in six patients were suspicious of anterior horn cell involvement (n = 3).

3.3.2. Additional investigations

Electroencephalography (EEG) was performed in 16/17 (94%) patients, in the youngest patient no EEG had been performed. In most patients (n = 15/16; 94%) focal (predominantly occipital), multifocal and generalized epileptiform activity was described; including spikes, waves, polyspikes, spike wave complexes and poly-spike wave complexes. Additionally, a slow background pattern (n = 11) and a photoparoxysmal-response (n = 7) was documented.

Polymyographies (EEG-EMG recordings) were performed in 7/17 (41%) patients, demonstrating a cortical origin of myoclonus in all patients. A short burst-duration of < 100 ms was reported, together with the presence of both positive and negative myoclonus. Back-averaging (n = 1) and cortico-coherence analysis (n = 1) supported the cortical origin of myoclonus.

Brain MRIs were performed in 14/17 (82%) patients (age performed 3–36 years) and were normal in all cases except for one, which showed cerebellar folia-atrophy around the age of 6 years.

3.4. Treatment of myoclonus and seizures

All patients were treated with one or more anti-epileptic drugs, with the aim of myoclonus suppression and seizure reduction. Only in the youngest patient clonazepam monotherapy was used to treat myoclonus. Combination-therapy consisting of clonazepam (17/17; 100%), valproic acid (16/17; 94%) and levetiracetam (11/17; 65%) was most frequently used. Although some patients reported an improvement with their medication regimes, in most of them myoclonus and/or seizures were still not satisfactorily controlled. For this reason, two patients were on a ketogenic diet [6]. Epilepsy severity rapidly progressed in one patient at age 8 years with 60–80 seizures during the night, which reduced to 20 seizures per night after starting the ketogenic diet. Four patients had undergone bilateral deep brain stimulation (DBS) in the Zona Incerta in the past (Anderson et al. [5]), only in one patient DBS was still active.

4. Discussion

Here, we describe detailed clinical and neurophysiological findings in a large NSPME cohort (n = 17). All patients tested carry the same homozygous *GOSR2* mutation (c.430G > T, p.Gly144Trp) and core-clinical features encompass early-onset ataxia, myoclonus and seizures with additional features including areflexia and scoliosis. Although the sequence of symptoms is identical in all patients, symptom severity and rate of progression varied considerably among individual patients, which is reflected by significant differences in seizure frequency and the wide range of the age of first wheelchair use (7–28 years).

Myoclonus is very prominent in all NSPME patients, interfering with mobility and daily activities. Negative myoclonus was clinically reported formerly, in this study we provide neurophysiological evidence for the presence of negative myoclonus [2]. This may well relate to the

reported frequent falls causing anxiety to walk and the use of a wheelchair. Noticeably, three patients in our cohort were diagnosed with hypothyroidism, which has not been reported previously in NSPME. Whether this belongs to the clinical phenotype or might for example be due to anti-epileptic drug use (e.g. valproic acid) is unknown, but clinicians should be alert to this non-neurological sign [13].

Over time, patients may additionally develop dysarthria and dysphagia. In contrast to the findings of Boissé Lomax and colleagues [2], in which patients developed dysarthria around their mid-to-late twenties, most patients in our cohort already had dysarthria during their first decade. In previous reports on NSPME, the age range of the included patients was 7–37 years. In our cohort, the youngest patient is 5 years old and the oldest 46 years old, indicating that despite the progressive and disabling nature of the disorder patients can survive into middle age. Previous reports on NSPME described cognitive function remains relatively preserved, with some memory problems and emotional lability reported around the third decade. In this study, we could not include substantial data on cognitive function in NSPME patients, but formal cognitive testing would be of great value in future studies.

Van Egmond et al. [4] previously reported sensory neuronopathy and anterior horn cell involvement in NSPME patients and our study builds on their findings. Although feasibility of NCS and needle EMG is challenging in NSPME patients due to their frequent myoclonus, we found that the H-reflex was absent in all patients (n = 9) and postulate three patterns observed: 1. A combination of sensory neuronopathy and anterior horn cell involvement 2. Anterior horn cell involvement without sensory neuronopathy 3. An isolated absent H-reflex, without other significant NCS and needle EMG findings. These groups suggest that grey matter disorganization of the spinal cord is more pronounced in one patient compared to the other. We speculate that anterior horn cell involvement explains areflexia in NSPME, as in our cohort needle EMG was aberrant in the majority of patients (n = 5/6), whereas relatively less patients displayed significant widespread sensory NCS abnormalities (n = 4/10). Neuropathology may facilitate further clarification of neuromuscular abnormalities and remains to be addressed in future studies on NSPME. Besides areflexia, it is unknown what influence neuromuscular involvement has on the phenotype in NSPME. In other conditions with anterior horn cell involvement such as Spinal Muscular Atrophies, scoliosis may be frequent [14]. Whether scoliosis and other deformities in NSPME are complications of neuromuscular involvement is left to be elucidated.

The clinical finding of areflexia and NCS- and needle EMG abnormalities demonstrate that the effect of *GOSR2* mutations is not confined to the central nervous system but also affects the neuromuscular system. Larson et al. described two sisters with hypotonia, progressive muscle weakness and CK values of up to ~5000. In the oldest sister, seizures were reported and muscle biopsy demonstrated an active dystrophic process with hypoglycosylation of alpha-dystroglycan. Targeted sequencing revealed compound heterozygous *GOSR2* mutations (c.430G > T and c. 2T > G) [11]. Moreover, Tsai et al. described a 36 week old male with compound heterozygous *GOSR2* mutations (c.430G > T and c.336 + 1G > A) with similar clinical characteristics. His muscle biopsy revealed severe non-dystrophic changes with normal levels of glycosylated alpha-dystroglycan [12].

Among the group of PMEs with cognitive preservation and the PMAs (Unverricht-Lundborg disease, ULD; *SCARB2*; *PRICKLE1*), NSPME appears to have the earliest age of onset [15–17] with a more progressive natural course compared to ULD for instance, in which a self-limited progression is evident [16]. Magaudda et al. [16] reported that 70% of their ULD patients were still able to walk independently in adulthood (n = 20; 26–53 years). In our NSPME cohort, (n = 17; 5–46 years), only 29% were still able to walk independently.

Quite similar to *SCARB2* [17], epilepsy severity markedly differs between individual patients in NSPME where only two patients did not experience seizures. One is the youngest patient of 5 years old and the other is a 13 year old boy. Although his EEG showed epileptiform activity and a photoparoxysmal-response, he has had no clinical seizures so far. He is treated for his myoclonus though and this may have influenced seizure onset. On the contrary, findings in two other patients illustrate epilepsy may be quite severe in NSPME, even at a young age. In one patient, epilepsy started at age 7 years and she experienced a rapid progression of seizure frequency, with up to 60–80 seizures during the night at age 8 years. This seizure severity has not been reported before in NSPME. The other patient developed an episode with increased seizure frequency and status epilepticus at age 26 years.

Fever and intercurrent illness appear to have a marked negative effect on symptoms in NSPME. Parents reported that motor function (e.g. walking) became more difficult during an episode of intercurrent illness in their child, and that they felt that after such an episode their children did not reach their previous level of motor functioning again. Moreover, parents and patients themselves reported myoclonus worsened during fever/intercurrent illness. For this reason in some patients a mitochondrial disorder was first suspected before the diagnosis NSPME was made. For patient counseling, it is important to recommend careful monitoring of fever and intercurrent illness and take preventive measures such as antipyretic therapy. Triggers identified for symptom exacerbation in NSPME overlap considerably with triggers found in patients with *ATP1A3, GNAO1* and *SCNA1* mutations. Besides factors such as stress and strong emotions, fever and increased environmental temperature have been reported to provoke or exacerbate symptoms in these conditions as well [18–22]. Particularly the latter factors raise questions with regards to what mechanism underpins the role of elevated body temperature and perhaps that of inflammation.

Although GOSR2 plays a crucial role in the secretory pathway during the fusion of vesicles with the cis-Golgi in eukaryotic cells, it is puzzling why mutations in *GOSR2* lead to a predominantly neurological phenotype. Jepson et al. postulated that in particular the nervous system is vulnerable to disturbances in ER-to-Golgi-trafficking due to its extensive volume of membrane trafficking. In addition, they hypothesized that *GOSR2* mutations may lead to an imbalance of ion channel activity attributable to defective post-Golgi trafficking of ion channels, subsequently influencing neuronal excitability and neurotransmitter release [23,24]. Recent work by Lambrechts et al. sheds further light on the predominantly neurological phenotype and suggests a role for glia in the pathophysiology of NSPME [25].

In conclusion, NSPME is characterized by a uniform sequence of early-onset ataxia, myoclonus and epilepsy with additional distinctive features including areflexia and deformities such as scoliosis. We report that there is a considerable variability in symptom severity and progression. Neurophysiological features regarding neuromuscular involvement in NSPME are also variable, but indicate involvement of the peripheral nervous system. Treatment options are symptomatic and do not satisfactorily control symptoms, which significantly influences daily functioning of patients with NSPME. Currently, our understanding of the *GOSR2* function is limited, and the mechanism behind the (mainly neurological) clinical phenotypes of *GOSR2* mutations even more so. Elucidating the exact function of *GOSR2* and the pathophysiology of *GOSR2*-related disorders hopefully contribute to a mechanism-based treatment of NSPME and related disorders.

Disclosures

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Declaration of competing interest

None of the authors report any conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2020.02.005.

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